HSRB Human Studies Review Board

Month Day, Year

H. Christopher Frey, Ph.D.
Assistant Administrator, Office of Research and Development
United States Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: May 16-18, 2023, EPA Human Studies Review Board Meeting Report

Dear Dr. Frey:

The United States Environmental Protection Agency (EPA) requested that the Human Studies Review Board (HSRB) provide scientific and ethics review of two research articles and a weight of evidence study involving human participants.

On July 26, 2023, the HSRB considered a weight of evidence for acute inhalation endpoints for formaldehyde exposure. The weight of evidence summary consisted of four studies reviewed by the HSRB. The EPA has proposed points of departure based on the weight of evidence.

The HSRB's responses to the charge questions for the three studies presented at the meetings, along with detailed comments and recommendations for the EPA to consider are provided in the enclosed final meeting report.

Sincerely,

Signature
Lisa Corey, Ph.D.
Co-Chair, HSRB

Signature
Julia Sharp, Ph.D.
Co-Chair, HSRB

Report of the U.S. Environmental Protection Agency Human Subjects Review Board

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AMSTAT Consulting

David Willams, Ph.D.
HSRB Science Reviewer
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EPA Contact

Tom Tracy, Designated Federal Officer

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List of Acronyms

Introduction

On May 18, 2023, the HSRB considered a weight of evidence for acute inhalation endpoints for formaldehyde exposure. The weight of evidence summary consisted of four studies reviewed by the HSRB. The EPA has proposed points of departure based on the weight of evidence.

Review Process

The Board conducted a public meeting on May 18, 2023. Advance notice of the meeting was published in the Federal Register as "Human Studies Review Board; Notification of a Public Meeting" (EPA, FRL-9328-01-ORD).

The Agency staff presented their weight-of-evidence review, with the presentation followed by clarifying questions from the Board. The HSRB considered public comments and then proceeded to address the charge question. Following discussion, the HSRB decided to convene a working group to further address EPA's charge question and meet again on July 26, 2023.

On July 26, 2023, the Board considered public comments and discussed the review of the HSRB Working Group. For the charge question, the Chairs called for the Board to vote to confirm concurrence on a summary statement reflecting the Board's response. This Final Report of the meeting describes the HSRB's discussion, recommendations, rationale, and consensus in response to the charge question.

For their evaluation and discussion, the Board considered materials presented at both meetings, both from the EPA and from the public comments, research articles, and related materials, the Agency's review, the Agency's statistical analysis of the research data, and oral comments from Agency staff during the HSRB meeting discussions. A list of materials reviewed is included as Attachment A. A comprehensive list of background documents is available at https://www.epa.gov/bosc/may-16-18-2023-hsrb-meeting.

Charge Questions and Context

Charge to the Board – Science

OCSPP has developed a weight of evidence for acute inhalation endpoints for formaldehyde that considered multiple studies and proposed acute inhalation PODs for 3 durations (15-min peak, 8-hr, and 24-hr PODs). Please comment on the use of the 4 studies reviewed by the HSRB (Kulle et al., 1987; Andersen and Mølhave, 1983; Lang et al., 2008; Mueller et al., 2013) in OCSPP's weight of evidence for acute inhalation endpoints and the proposed PODs in Table 3.

HSRB Response

In general, the four studies (Kulle et al., 1987; Andersen and Mølhave, 1983; Lang et al., 2008; Mueller et al., 2013) summarized in the charge document appear to be appropriate for use in a WOE for determining PODs relative to formaldehyde; the EPA should consider limitations that the HSRB has identified. EPA should consider specific HSRB comments and recommendations in their weight of evidence examination.

Science Review

Formaldehyde is an aliphatic aldehyde known to cause acute and chronic exposure effects. It has been variously registered under the Federal Insecticide Fungicide and Rodenticide Act (FIFRA) as a disinfectant and material preservative. It has also been registered under the Toxic Substances Control Act (TSCA) as a reactant utilized in various formulations.

Formaldehyde has several recognized sensory irritant effects from acute air exposure, including eye irritation, nasal irritation, and throat irritation. It has also been shown to cause reduced pulmonary function with chronic exposure.

EPA's Office of Chemical Safety and Pollution Prevention (OCSPP) has been tasked with developing acute and short-term inhalation points of departure (PODs) for formaldehyde. In addition to the systematic review conducted by EPA's Integrated Risk Information System (IRIS) Program, OCSPP examined additional studies for potential use in deriving PODs at 15-min, 8-hr, and 24-hr exposure durations.

EPA IRIS defines an adverse effect as follows: A biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge.

EPA IRIS defines an acute exposure as: Exposure by the oral, dermal, or inhalation route for 24 hours or less.

Four studies reviewed by the HSRB are the focus of this report. Further, two additional studies which were not reviewed by the HSRB were used by EPA in its WOE. Summary effects are highlighted and summarized in Table 2 of the charge document. These studies are briefly summarized below.

Kulle et al., 1987

This was a controlled human exposure study (n = 19) investigating sensory irritation at three time points (before, during, and after) exposure. Exposure concentrations ranged from 0.5-3.0 ppm, with subjects generally reporting mild-to-moderate irritation at higher doses.

- The HSRB determined that the research described …is scientifically sound, providing reliable data for use in a weight-of-evidence to determine a POD for acute inhalation exposure to HCHO provided that the recommendations provided by the HSRB are considered.
- Based on its review, the HSRB ...does not find that the research described… provides clear and convincing evidence that the conduct of the research was fundamentally unethical or deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent.
- EPA IRIS rated the confidence level of this study medium.

Andersen and Mølhave, 1983

This was a controlled human exposure study (n = 16) investigating self-reported irritation using a 0-100 scale score (100 highest discomfort). Exposure concentrations ranged from 0.24-1.61 ppm for a 5-hour duration over four days. Discomfort was generally reported at higher dose levels after prolonged exposure (4-5 hours).

- Owing to the inclusion of some smokers in the study along with analytical issues and lack of available data, some endpoints could not be evaluated. However, the HSRB determined that the research described ….provides scientifically sound data for qualitative use in a weight-of-evidence to support the determination of a POD for acute inhalation exposure to formaldehyde, given the limitations and recommendations provided by the HSRB are considered.
- Based on their review, the HSRB ...does not believe that the research described …provides clear and convincing evidence that the conduct of the research was fundamentally unethical or deficient relative to the ethical standards prevailing at the time the research was conducted in a way that placed participants at increased risk of harm or impaired their informed consent.
- EPA IRIS rated the confidence level of this study medium.

Mueller et al., 2013

This was a controlled human exposure study (n = 41) in non-smoking adult male subjects who were categorized into two groups (hypo- or hypersensitive) investigating a combination of responses (e.g., conjunctival redness, tear film, nasal flow, etc.) and a questionnaire. Exposure concentrations ranged from 0.3-0.7 ppm (with peaks at lower concentrations) administered over 4 hours on 5 occasions. Nasal flow rates increased in hypersensitive individuals at higher doses. A performance evaluation survey score indicated a linear increase in outcomes for hypersensitive individuals.

- The HSRB determined that the research described … provides reliable semi-quantitative data for use in a weight-of-evidence to determine a point of departure for acute inhalation exposures to formaldehyde, given the recommendations by HSRB are considered.
- Based on their review … the HSRB has determined that the conduct of the research was not fundamentally unethical, that the research was not deficient relative to the ethical standards prevailing at the time the research was conducted and was NOT conducted in a way that placed participants at increased risk of harm or impaired their informed consent.
- EPA IRIS rated the confidence level of this study high.

Lang et al., 2008

This was a controlled, human exposure study (n = 21) in non-smoking adults investigating a combination of responses (e.g., blinking frequency, conjunctival redness, nasal flow, etc.) and a questionnaire. Exposure concentrations ranged from 0.15-0.5 ppm, with peaks up to 1.00 ppm at the highest concentrations, administered over four days. Discomfort was reported most often at higher doses, with “anxious” participants reporting more discomfort complaints.

- Response to science charge question: The HSRB agrees with EPA that the study … is scientifically sound and provides reliable data for use in a weight-of-evidence analysis to determine a point of departure for acute inhalation exposures to formaldehyde, given the recommendations by the HSRB are considered.
- Response to the ethics charge question: Based on the review … the HSRB has determined that the conduct of the research was not fundamentally unethical. The HSRB has also determined that the research was not deficient relative to the ethical standards prevailing at the time the research was conducted and was not conducted in a way that placed participants at increased risk of harm or impaired their informed consent.
- EPA IRIS rated the confidence level of this study high.

The EPA considered two other studies when determining the PODs. HSRB members were not asked to review them because they are not intentional human exposure studies. Though the HSRB did not formally review these studies, the HSRB working group provides a brief summary of them both for completeness in the context of evaluating the proposed WOE.

Hanrahan et al., 1984

This was a cross-sectional survey of mobile homes in Wisconsin (n = 61 completed health surveys) conducted in 1979. Air samples were taken in a closed home (i.e., gas appliances turned off and windows closed $\geq$ 30 minutes) during a single 1-hour period. Sensory irritation questionnaires were completed by participants blinded to their level of exposure. Median concentrations in the air samples were 0.16 ppm (range < 0.1 ppm - 0.8 ppm). Presence of smokers and gas appliances were not found to be significant contributors to exposure concentrations. Respiratory irritation was reported by participants (e.g., 34% reported runny nose; 33% dry/sore throat; 28% coughing; 28% ocular irritation; and 26% burning eyes). A significant positive relationship between concentration and reported eye irritation was found. Demographic analyses were limited, as only 30 participants reported their demographic characteristics.

- EPA IRIS rated this study as a confidence level of medium.

Liu et al., 1991

This was a natural exposure study of mobile homes in California in summer 1984 (n = 663 households, n = 1394 residents) and winter 1985 (n = 523 households, n = 1096 residents). Indoor monitors were provided to participants, who were instructed to place one in the primary bedroom and one in the kitchen for a single one week monitoring period. Self-reported questionnaires on occupants and household characteristics were also collected. Mean concentrations averaged across the households were 0.089 ppm in summer and 0.088 in winter (range from < 0.01 ppm to 0.46 ppm). Generally, symptoms reported on the surveys were higher for smokers, females, and those with chronic respiratory

health issues. In summer, the top reported symptoms in females were headache (26.2%), cough (19.8%), and running nose/sleeping problems (tied at 19.4%) and for males were running nose (16.1%), headache (14.9%), and cough (14.3%). In winter the top reported symptoms in females were headache (25.5%), cough (24.6%), and running nose (22.5%) and in males were cough (21.2%), running nose (20.6%), and headache (14.4%). The percentage of respondents with burning and tearing eyes was shown to be positively associated with formaldehyde exposure (ppm X hours).

- EPA IRIS rated this study as a confidence level of medium.

EPA chose to use the BMC/2 (where BMC is the benchmark concentration, the estimate for the concentration at which the extra risk is 10% above clean air exposure group) for eye irritation from Kulle et al. (1987) as the basis of the 15-minute peak exposure. The BMC/2 for eye irritation based on Kulle et al. (1987) was also the basis for the 8-hour POD; however, a duration adjustment was made. The exposure duration in Kulle et al. (1987) was 3 hours and EPA chose a duration adjustment based on evidence of Haber's Law suggested by Anderson and Molhave (1983). Hanrahan et al. (1984) was used as the basis of the 24-hour POD.

Comments

The HSRB offers comments followed by specific recommendations for EPA.

Endpoint

- Given EPA's definition of an adverse effect, the HSRB is unclear on the use of the term "adverse" to describe sensory endpoints (e.g., eye irritation) versus acute human-health exposure risk (e.g., lung injury).

Studies Used

- The scientific validity of each study relies upon the determination of whether it was conducted ethically. The submitted materials associated with the four chamber studies supported a determination that the conduct of the research was not fundamentally unethical and not deficient relative to the prevailing ethical standards at the time of each study.
- HSRB was not initially charged with reviewing Hanrahan et al. (1984) and Liu et al. (1991). Based on the current charge to the HSRB, a brief review of these studies was necessary to comment on EPA's use in a WOE. These two studies did not receive the same level of full HSRB review of science, statistics, and ethics as the four chamber studies.
- Observational studies like Hanrahan et al. (1984) and Liu et al. (1991), which are not controlled, replicable laboratory studies, do not seem to support the use of a quantitative POD calculation. Chamber studies like Kulle et al. (1987) and Lang et al. (2008) have stronger justification for use in a weight-of-evidence study.
- Hanrahan et al. (1984) state that the original intent of their study was to overcome the shortcomings of other self-report studies by using a "randomly selected and representative cross-section of mobile homes in Wisconsin" (p. 1027). Interestingly, this seems not to have

been successful, as the authors note that "the participation rate resulted in a sample which could not be considered representative of all Wisconsin mobile homes" (p. 1027).

- Liu et al. (1991) reported mail-in surveys, but also a subsample of home visits occurred (20% in summer and 14% in winter). It is not clear if results were impacted by potential differences between in-home and mail-only participants.
- Some reservations are acknowledged with the Mueller et al. (2013) study owing to the inability to obtain data and questions arising from analyses, hence making this study reliable as a semi-quantitative data source for use in WOE POD determination (as advised by the HSRB at the May 2023 meeting). Likewise, data were not available for Lang et al., 2008, though it was determined by the HSRB that it was scientifically sound and that it provides reliable data for WOE POD determination.
- As noted by EPA and public commenters, other agencies have chosen to use other studies as the basis of acute exposure guidelines. WHO, ACGIH, and EU SCOEL used Lang et al. (2008) with support of other studies. Other agencies have also opted to use low or no uncertainty factor in their assessments based on Lang et al. (2008).

POD Derivation Assumptions

- Haber's Law is the principle that incidence and/or severity of an effect is a product of concentration of the chemical and duration of exposure. EPA determined that low levels of HCHO follow Haber's Law (based on one study: Andersen and Mølhave, 1983), while higher concentrations do not. The assumption that low levels of HCHO follow Haber's Law led EPA to apply duration adjustments to the 8-hour PODs and in the WOE for the 24-hour PODs.
- Other EPA actions have concluded that HCHO does not follow Haber's Law. AEGLs were not adjusted for duration and EPA states that "...sensory irritation has been demonstrated to be an acute phenomenon, and IRIS concluded that the magnitude or severity of symptoms did not worsen over periods of prolonged exposure at a given concentration…" (p. 16 WOE document).
- The HSRB has not evaluated the full breadth of the literature on HCHO duration response. However, based on the four chamber studies evaluated in our review, there is no support for a duration adjustment.
- The HSRB disagrees that Anderson and Molhave (1983) is sufficient to support Haber's Law for HCHO and a duration adjustment, particularly given the existing literature demonstrating that HCHO does not follow Haber's Law.

Recommendations

- HSRB recommends that EPA conduct a more coordinated approach with other entities (e.g., NASEM, TSCA SACC) regarding advice in establishing PODs for HCHO as well as reviewing recommendations from these and other entities on HCHO exposure.To further this recommendation, the HSRB recommends that the EPA share this HSRB report with the NASEM and TSCA SACC, and that EPA consults with other State and Federal agencies as appropriate working on HCHO guidance/regulations.

- HSRB recommends that EPA provide clarification on the use of sensory endpoints as adverse effects in the context of this WOE review. In particular,
    - EPA should consider that PODs for sensory irritation could be used as a lower bound for potential adverse effects.
    - Additionally, HSRB recommends that no uncertainty factor is necessary when the POD is based on sensory irritation.
    - Finally, the HSRB agrees with evidence presented during public comments that younger individuals are more sensitive to sensory irritation than older individuals, and therefore younger individuals are an appropriate population for intentional exposure studies when sensory irritation is the primary objective. The definition of 'younger' should be established based on scientific research related to formaldehyde or other related chemical exposures; for example, Wysocki, Cowart, and Radil (2003) showed that sensory irritation sensitivity decreases with age, and that the decrease occurs in the 5th decade of age.
- HSRB recommends EPA clarify and justify its use of the BMC/2 from the Kulle et al. (1987) study to determine the 15-minute and 8-hour PODs. Specifically,
    - The BMC/2=0.34 (0.694/2; p.39 of ICF statistical analysis document) value from the Kulle et al. (1987) article was for a 3-hour exposure period. EPA should justify why this is a valid value to use for 15-minute peak exposure.
    - EPA states: "Therefore, although the BMC approach taken by IRIS is not common practice, OCSPP will rely upon the values generated by IRIS when considering acute points of departure" (charge document, p. 13 of 19). It is unclear what is meant by "common practice" and how the BMC/2 differs. In the ICF statistical analysis of Anderson and Mølhave (1983) from the October 2022 HSRB materials, Dr. Jonathan Cohen noted (p. 25) that the denominator of '2' in the calculation of BMC/2 was arbitrary and further offers a demonstrative example of the implications of this adjustment.
    - Additionally, BMC should be stated as BMC_{10} in all documentation.
- HSRB disagrees with EPA's assumption of Haber's Law for HCHO and recommends that EPA not make duration adjustments to develop the PODs. EPA should consider their previous approach to derive exposure criteria for chloropicrin whereby uncertainty factors were removed and the evaluation was conducted for younger individuals (EPA 738-R-09-308).
- Of the studies the HSRB evaluated, the controlled chamber studies (e.g., Mueller et al. (2013) and Lang et al. (2008)) have preferred study design and greater scientific rigor than the observational studies (e.g., Hanrahan et al. (1984) and Liu et al. (1991)). Public comments

provided a summary comparison of the two types of studies in the context of this review; the HSRB appreciates the detail in the presentation. HSRB recommends that EPA use exposure levels from chamber studies rather than observational studies.

- The Hanrahan et al. (1984) study states that it was not representative of Wisconsin where it was originally conducted. EPA should provide a rationale as to the value of this study as representative (or not) for determining adverse human exposure generalizable across the entire U.S.

- EPA should provide justification for relying on both self-report, cross-sectional studies and intentional exposure studies for the proposed WOE PODs, when the scientific rigor differs between these study types. In particular, EPA states that "TSCA requires that…EPA must use scientific standards and base those decisions on the best available science and on the weight of the scientific evidence. EPA also states that the weight of evidence may include considerations of the data quality "and the extent to which effects can be replicated with a laboratory and across different laboratories" (EPA WOE Presentation, May 2023).

Recommendations for Future Studies

The HSRB strongly recommends that the EPA clarify the scope of HSRB review and how their review will be used in conjunction with other efforts within and external to the EPA. This clarification includes clearly communicating the charge question to the HSRB, as well as noting when and how each individual review will be used as part of a larger effort (e.g., a weight-of-evidence).

Attachment A
Materials Reviewed

1a. Andersen and Molhave 1983.pdf
1b. EPA Science Review - Andersen and Molhave.pdf
1c. Ethics Review Anderson and Molhave.pdf
2a. Kulle 1987.pdf
2b. Kulle 1993.pdf
2c. EPA Science Review - Kulle.pdf
2d. EPA Ethics Review Kulle.pdf
EPA Science Review Anderson & Kulle w Formaldehyde Overview for HSRB.pdf
Ethics Review - Andersen and Molhave.pdf
Ethics Review - Kulle.pdf
Statistical review of Anderson and Kulle studies. 090522.pdf
1a. Mueller 2013.pdf
1b. EPA Science Review - Mueller DER.pdf
1c. Statistical Report_Lang and Mueller_02.21.23.pdf
1d. EPA Ethics Review - Mueller.pdf
1e. Online Resource 1 SPES.pdf
1f. Online Resource 2 PANAS.pdf
1g. Online Resource 3 Conjunctival Redness-both.pdf
1h. Online Resource 4_ConjRed Hypo.pdf
1i. Online Resource 5_ConjRed Hyper.pdf
1j. Online Resource 6 Eye blinking freq.pdf
1k. Online Resource 7 sBUT.pdf
1l. Online Resource 8 nasal flow.pdf
1m. Online Resource 9 SPES sum score.pdf
1n. Online Resource 10 SPES eye irritation.pdf
1o. Online Resource 11 SPES nasal irritation.pdf
1p. Online Resource 12 SPES olfactory symptoms.pdf
1q. Online Resource 13 SPES impure air.pdf
2a. Lang 2008.pdf
2b. EPA Science Review - Lang DER.pdf
2c. Statistical Report_Lang and Mueller_02.21.23.pdf
2d. EPA Ethics Review - Lang.pdf
4b. EPA IRIS Toxicological Review of Formaldehyde – Inhalation April 2022.PDF
EPA HSRB Letter_HAK (003).pdf
Excerpts of Key Public Comments Relevant to HSRB Review_051223 FINAL.pdf
Formaldehyde HSRB slides 5_18_2023.pdf
HSRB 5-16-2023 Ethics Review Mueller et al Final.pdf
HSRB 5-17-2023 Ethics Review Lang et al.pdf
HSRB 5-17-2023 Lang et al Science Review.pdf
HSRB 5-18-2023 WOE acute inhalation HCHO discussion.pdf
HSRB Presentation _Sahar Osman-Sypher 051823.pdf
HSRB Science Slides May 2023-5-16 Overview Mueller.pdf
HSRB Woods Comments 5.18.23.pptx
Kaden Comments to HSRB on Lang study_Day 2.pptx

Kaden Comments to HSRB on Mueller_Day 1.pptx
Kaden Comments to HSRB on WOE.pptx
Kaden Critique of Hanrahan 1984.pdf
Lang et al Subject information and ICF template.de.en.pdf
Sherman EPA HSRB Evidence Integration March 18 2023 Final.pptx
Sherman EPA HSRB Sensitive Subpopulation March 17 2023.pptx
Sherman May 18 2023 HSRB WOE Presentation and Written Version of Oral Comments.pdf
Sherman Presentation for EPA HSRB March 16 2023 Final.pptx
ACC FA Panel Letter to HSRB_June 21 2023.pdf
Hanrahan.pdf
Liu.pdf